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McNeil, Ft. Washington: FDA Case Study

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ABSTRACT

This research analyzes the Food and Drug Administration's (FDA) quality systems methodology through a detailed 12-year case study of McNeil Consumer Healthcare and its Ft. Washington, Pennsylvania manufacturing facility. This in-depth review, from 2000 to 2011, includes plant inspections reports, out-of-compliance findings, warning letters and a plant closure injunction. It then contrasts the specific findings of the McNeil case study with an analysis of overall FDA performance within the same sector of Finished Bio-Pharmaceuticals (BP). In addition, this case study pays particular attention to the role played by the FDA's risk methodology in enhancing the overall inspection process and increasing its quality assurance.

Keywords: FDA, CAPA, cGMP, enforcement, warning letters, pharmaceuticals.

FOOD AND DRUG ADMINISTRATION CASE STUDY

The FDA is the supervisory agency that provides oversight and guidance to the biopharmaceutical (BP) industry. It safeguards the public by ensuring that BP products are safe, effective, and manufactured in accordance with current Good Manufacturing Practice (U. S. Food and Drug Administration, 2004a). This paper provides a case study of McNeil Consumer Healthcare and its main manufacturing facility at Ft. Washington, Pennsylvania, from 2000 to 2011. Over this 12-year period, the case study details FDA activities at this site. This includes plant inspections, Form 483 observational reports (483), and warning letters (WLs), as well as recalls and plant closures. While it would be premature to extrapolate from one case study to overall FDA performance, it is fair to say that certain insights can be gained concerning procedures, performance, oversight, and governance. Similarly, these findings about FDA performance provide an opportunity to review how its newly adopted risk methodology and quality assurance practices are incorporated into its oversight practices.

To put this case study into appropriate perspective, the findings were compared with other research that focuses on more quantitative studies of FDA performance using sector-wide data. The two principal academic investigations of FDA and quality assurance (QA) that we are aware of are Adis' risk studies (2007; 2008), and Marcher and Nickerson's (2006) review of quality systems. Both were sector evaluations, rather than a case study.

The McNeil Ft. Washington facility is noteworthy in that it posed significant compliance challenges to the FDA during the 12-year period. There were several FDA Field Alerts about

failed manufacturing processes and several large scale recalls of such popular product as Motrin, Tylenol, and Listerine.

The problems at this site have caused the FDA to take the unusual step of making available the Establishment Inspection Reports (EIRs) for this facility. With these reports, one can track FDA interactions with the Ft. Washington site and review FDA oversight and plant compliance (Betterchem, 2008). In other words, the researcher has an insider's picture of quality assurance and risk prevention activities at Ft. Washington.

The FDA rarely makes EIRs available because it respects manufacturers' concerns about releasing proprietary and confidential information. In addition, part of its mandate is to provide guidance, so a non-adversarial environment is preferred. Therefore findings from EIR plant inspections are regularly withheld, even from the provisions of the Freedom of Information Act (U. S. Food and Drug Administration, 2008a). But in this instance, due to the seriousness of the infractions at the McNeil site, the FDA has released the 12-year history of inspections and oversight. Though this material has been heavily redacted to maintain confidentiality, it is still a valuable resource. Furthermore, due to the extent and flagrance of the violations, there are additional public documents: a consent Decree to close the Ft. Washington plant, transcripts of the FDA testimony at congressional hearings about McNeil's recalls, and public statements from McNeil's management and their parent company Johnson and Johnson. These were helpful in piecing together the activities of the principals, during this time period of 7 major recalls.

The Center for Drug Evaluation Research (U. S. Food and Drug Administration, Center for Drug Evaluation and Research, 2007) is the FDA agency directly responsible for the Finished Pharmaceuticals sector that includes over-the-counter drugs. It has thousands of employees and performs hundreds of inspections per year. Consequently, this case study review can be only a very narrow investigation into its quality assurance activities. By reviewing the data in this case study, the research is establishing some anecdotal evidence about CDER performance and its use of quality assurance techniques. To broaden the findings, the research then looked at CDER's activities and performance at inspection sites throughout the sector.

BACKGROUND: MCNEIL CONSUMER HEALTHCARE, FT. WASHINGTON

McNeil is a large sophisticated BP company that manufactures, packages, distributes and markets a range of pharmaceutical products including the over-the-counter drugs Tylenol and Motrin. Its annual sales in 2004 were US \$2.1 billion. Its headquarters and major manufacturing facility employs 2,600 people and is located in Ft. Washington, Pennsylvania. The plant as a manufacturer of finished pharmaceuticals must meet the FDA current good manufacturing practices (cGMP). These guidelines are the basis for the quality assurance (QA) activities, and act as a barrier against manufacturing failures (U. S. Food and Drug Administration, Center for Drug Evaluation and Research, 2009).

Yet, throughout this case study time period, QA problems at Ft. Washington caused McNeil to notify the FDA on the necessity of issuing Field Alerts and Recalls. For instance, in the 2008-2010 period, there were two major recalls from the Ft. Washington plant involved the

production of Motrin and Children's Tylenol, resulting in more than 100 million bottles being pulled from the distribution channel (U. S. Food and Drug Administration, 2011b). Many consider this one of the largest recalls of child medication in FDA history.

This triggered an FDA site inspection which found significant quality-control problems and detected metallic particles in the children's medications. Based on this inspection, McNeil recalled an additional 136 million bottles of pediatric medications, and ceased production.

During this same period, McNeil faced additional recalls of certain medications. These included Benadryl, Motrin, adult Tylenol and Zyrtec products from the Ft. Washington site. The cause for these multiple recalls was the chemical breakdown of a protective coating on wooden transport pallets causing a moldy odor. This was absorbed by the pharmaceuticals products.

It should be noted that a recall by definition is a flagrant QA violation in which there is a reasonable probability that the use of or exposure to a violative product will cause serious adverse health consequences or death. The majority of McNeil's recalls are Class I, the most serious category.

One of the more telling events occurring at the end of the study period was the McNeil Consent Decree of Permanent Injunction (United States v. McNeil, 2011). The basis of the Decree was that McNeil and certain corporate officers had allegedly manufactured, processed, packed, labeled, held, and distributed drugs that were in violation of cGMP. The Decree names the McNeil Corp of New Jersey, which does business in Pennsylvania and elsewhere, and key defendants such as the VP of Quality Control and the VP of Operations. The Decree permanently restrained and enjoined McNeil to stop activities at Ft. Washington until cGMP were certified as restored. McNeil consented to this without admitting or denying the allegations, yet immediately shuttered the Ft. Washington facility.

The United States Congress did not regard these recalls as trivial events, and began their own investigation into the FDA—McNeil situation. Without a doubt, the scale of the recalls and the popularity of the drugs involved, caused Congress to want to know more about McNeil's quality controls, as well as the FDA's supervisory oversight (Sharfstein, 2010). This investigation most likely was instrumental in having the FDA release the previously classified Ft. Washington site inspections reports. The release of these documents allowed the congressional committee, as well as researchers, to probe quality assurance activities at both the FDA and McNeil for the last 12 years.

FDA'S cGMP

The FDA functions as the responsible supervisory agency to the BP industry, mandating quality systems (GAMP, 2003) in all aspects of the manufacturing life cycle of drugs, vaccines, and other biological products. Its oversight tasks are to inspect facilities to ensure that industrial standards for purity, potency, and quality for drug manufacturing are maintained. The agency examines biological products and manufacturing processes, issues warning letters, and takes enforcement action, such as ordering recalls. The regulatory guidelines (U. S. Food and Drug

Administration, 2003a & 2004a) have an exceptionally low tolerance for variability or nonconformity in all pharmaceutical products and processes.

These oversight tasks continue to grow as the number of BP research and production sites become more numerous. Yet the Agency's resources have not expanded proportionally, consequently its resources are constrained. It has a limited budget, and is understaffed, and possibly not fully trained to meet the new technologies in the BP industry. These inadequacies prevent it from meeting its goals of inspecting domestic BP facilities on a regular basis. More specifically, it cannot meet its mandated 2 year inspection cycle, or its 4 year cycle for more complex products and processes. This dearth of resources if not addressed, will create either an increasing backlog of site inspections on one hand, or on the other hand, more partial inspections.

To meet this supervisory bottleneck, the FDA chose to supplement its industrial best practices inspections with a quality assurance methodology that orders and prioritizes BP sites based on their associated risk (U. S. Food and Drug Administration, 2004b). This transition began in 2004, when the agency adopted this new risk-based methodology, outlined in part by the Pharmaceutical Current Good Manufacturing Practices (cGMP) for the 21st Century (U. S. Food and Drug Administration, 2004a).

This methodology streamlines the oversight process, choosing manufacturing facilities with the highest risk priority, pinpointing the focus for the site inspection, and determining whether warning letters and recalls are necessary (U. S. Food and Drug Administration, 2008b). "The model is based on a risk-ranking and filtering method that is well-recognized, objective, and rigorously systematic. The Agency believes that this methodology makes the best use of its limited surveillance and enforcement resources, while maximizing the impact of those resources on the public health" (U. S. Food and Drug Administration, 2004a).

More specifically, this research analyzes the role of quality assurance as detailed in the cGMP regulations. Prominent within these are the concepts of corrective and preventative action (CAPA) for risk management. CAPA is a critical component for sustainable compliance since problem prevention, containment, and remediation are intrinsic in determining the outcome (COSO, 2004). In this new rubric, site inspectors use the CAPA component to help monitor system performance, record keeping, staffing qualifications, and quality assurance (ICH, 2005; U. S. Food and Drug Administration, 2003b & 2006).

As part of this ongoing CAPA process, the FDA increments their normal inspection schedule with priority inspections for those manufacturing sites that have a previous history of nonconforming production practices, or perform processes that have an inherently higher risk of system failure (U. S. Food and Drug Administration, 2008c). In this way, the FDA builds a performance history for each manufacturer, focusing on these risk management statistics (ICH, 2007):

- Overall compliance status and history of the company and facility
- Results of the company's quality risk management activities
- Complexity of the manufacturing process
- Complexity of the product and its therapeutic significance

- Number and significance of quality defects (e.g., recalls)
- Results of previous audits/inspections

One of the research tasks is to analyze McNeil inspection documents to judge the effectiveness of the CAPA risk management methodology during the 12-year period.

RESEARCH METHODOLOGY

The researchers examined the FDA reports about the McNeil Ft. Washington facility, and paid particular attention to those issues that dealt with cGMP, quality assurance and CAPA. As mentioned in the previous section, the research looked into FDA performance, judged by frequency and depth of the inspections, violations cited, and the guidance given by the FDA. This was then contrasted against the actual field alerts, recalls and plant closing. The basic question for the research is - Did the FDA provide sufficient CAPA oversight? The corollary being - With more oversight could these events be eliminated?

Using published documents and the Freedom of Information Act, the research was able to review FDA activity that met the following criteria:

- Took place at the McNeil Ft. Washington facility during 2000-2011 time period.
- Subject was cGMP found in regulations 501(h) of the Act (21 U.S.C. §351(h)) (U. S. Food and Drug Administration, 2008c)
- Specifically addressed cGMP Practice for Finished Pharmaceuticals
- QA and CAPA risk methodology as mentioned directly or indirectly in FDA regulation Part 211.

Within this framework, the researchers reviewed in detail the supervisory activities of the FDA relating to the Ft. Washington facility. These activities are listed in in Table 1, with the first column being the common name used by the FDA, followed by a brief definition (U. S. Food and Drug Administration, 2008c). For the most part they are self-explanatory, though the more important ones, such as warning letters (WLs), will be further developed as the paper proceeds. It should be noted that for the most part, the referenced activities in the table are in logical order of growing importance. Category 1 contains CAPA activities to correct and prevent production problems. For instance, the EIR report documents the inspection. This is followed by an observation Form 483, listing objectionable conditions found during the inspection. The last entry in this category is the Warning Letters (WLs) for violations of regulatory significance, and establishing prior notice before judicial action.

This grouping is followed in the table by Category 2, another class of CAPA activities that focusses on alerting the distribution chain about problems of non-conforming batches of drugs. This is done when the manufacturer, in collaboration with the FDA, issue field alerts (U. S. Food and Drug Administration, 2011a), and if necessary recalls products.

Category 3 addresses the most serious FDA enforcement activities: consent decrees to halt manufacturing and full plant closure. When the FDA realize that their CAPA activities have

failed to eliminate hazards, they turn to the courts for legal action such as requesting an injunction to temporarily stop production, or to close manufacturing operations. These enforcement actions are sometimes bypassed when the manufacturer voluntarily closes the plant to attempt to avoid the negative publicity of an FDA closure.

Category 1	FDA Corrective and Preventive Activities
EIRs	Establishment Inspection Report: The EIR documents the inspection. FDA guidelines establish a 2-4 year manufacturing inspection cycle, plus additional inspections based on risk evaluation.
483s	FDA Form 483: A summary of objectionable conditions listed in the EIR or related documents which are cited to support specific regulatory recommendations. These become the basis for WLs.
WLs	Warning Letters are issued only for violations of regulatory significance. Significant violations are those that may lead to enforcement action if not promptly and adequately corrected. WLs are the agency's principal means of achieving prompt voluntary compliance and establishing prior legal notice.
Category 2	FDA and Manufacturer CAPA Remediation Activities
Field Alerts	A manufacturer is required to file a Field Alert when an anomaly occurs in the manufacturing, viz., testing, processing, packing, labeling, storage, or distribution of a licensed biological. In particular those anomalies in which the safety, purity, or potency of a distributed product may negatively impact the public health. Certain Field Alerts may escalate to recalls of distributed products.
Recalls	Recalls are actions taken by a firm to remove a product from the market. Recalls may be conducted on a firm's own initiative, by FDA request, or by FDA order under statutory authority. A recall means there is a reasonable probability that the use of or exposure to a violative product will cause serious adverse health consequences.
Category 3	FDA Enforcement
Consent Decree	Consent Decree of Permanent Injunction. An agreement by a defendant to an action to discontinue all activities viewed by the government as being illegal. This agreement occurs with the consent of both parties to the action and has court approval but stops short of a definitive judicial determination.
Plant Closing	An example is the voluntary plant closing by McNeil and Johnson and Johnson's management, prior to the issuance of the Consent Decree.
Category 4	Congressional Investigative Activities
Congressional Investigation	Congressional Committee on Oversight and Government Reform hearing on FDA oversight of McNeil.

Table 1: Review of Major FDA Topics.

The final category is congressional investigative activities. These investigations are only initiated where the number and type of recalls are significant. In this instance, Congress chose to review the FDA-McNeil business interactions.

Of all the items listed in Table 1, the researchers were particularly interested in how the CDER uses Warning Letters (WLs), since it is one of the stronger enforcement mechanisms. By formally establishing prior notice, the WL has the ability to both warn and guide manufacturers to correct significant regulatory violations. As the FDA states, "(A) Warning Letter is the agency's principal means of achieving prompt voluntary compliance with the Federal Food, Drug, and Cosmetic Act (the Act)." (U. S. Food and Drug Administration, 2012)

Furthermore, much can be learned by the CDER criteria for issuing WLs:

1. The violation reflects a history of repeated or continual conduct during which time the firm has been notified of a similar violation
2. There is a violation of cGMP in terms of manufacturing, ingredients, dosage, quality systems and oversight
3. The product contains illegal pesticide residues
4. The product shows short contents, subpotency, or superpotency

It is easy to see why WLs are a critical enforcement tool for the FDA in dealing with manufacturing QA failures. The WLs, together with the other McNeil related documents, present a dynamic picture of interactions between the FDA and the McNeil during this 12 year period.

ANALYSIS

In 2010 McNeil voluntarily closed the Ft. Washington plant. This closing took place while a court ordered injunction to cease manufacturing was in its initial phases of the proceedings. In the following year a congressional investigation began into the interactions between the FDA and McNeil. Its initial focus was on their latest recalls, but expanded into other areas over time.

In a similar way, this research seeks to understand the level of oversight and guidance shown by the FDA to McNeil in this time period.

To address these issues, the researchers summarized the FDA-Ft. Washington interactions between 2000-2011 (see Table 2). The data in the table ranges from EIR Inspections to Recalls, and from Consent Degree to Congressional Investigation. In this way the data represents a time chart showing the correspondence between CDER activity and QA problems at the Ft. Washington plant.

Table 2 shows that CDER addressed the Ft. Washington QA issues with 13 inspections, rather than the 3 or 4 that is typical for a well-functioning plant over a similar time period. The inspections were detailed enough to generate seven 483 Reports for objectionable conditions. The inspectors determined in many instances the root causes of these problems stemmed from the cGMP areas of QA and CAPA. So in one sense, the CDER did its job with guidance and ever stricter oversight. Furthermore, in reading those EIR reports, particularly in the years 2000-2007, one can loosely conclude that McNeil remedied those reported quality control conditions, improved their best practices and minimized or eliminated any previously stated objectionable conditions. This was demonstrated by several years with either no inspections, or inspections with no 483 reports of objectionable conditions.

However, this preliminary interpretation may be incorrect in light of the serious QA problems that occurred later in 2008-2011. Researchers know that QA and risk avoidance methodologies are built on sustainable manufacturing practices, or what Booch (1994) calls “industrial strength” systems. The fundamental feature of an industrial strength system is day-in day-out quality and reliability throughout the life cycle of production. Manufacturing quality problems do not

suddenly materialize but are the result of failures over time. So it is a concern that the 483s, field alerts, and recalls of the earlier time period 2000-2002 are in fact repeated in the later 2008-2010 period.

	Years												
	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	Total
Category 1 CAPA Activities													
EIRs	1		1	2	2		2		1	2	3		13
483s	1				1		1		1	1	2		7
WLs													0
Category 2 CAPA Remediation													
Field Alerts	2												2
Recalls		1	1						1	2	2		7
Category 3 Enforcement													
Consent Decree												1 Mar.	1
Plant Closing											1 Apr.		1
Category4 Investigative													
Congress Investigation											1		1
Totals	4	1	2	2	3	0	3	0	3	5	9	1	

Table 2: Summary of CDER McNeil Activity.

With this in mind, the researchers reviewed the same data on a more granular level by looking at three periods: the early years (2000-2002), the mid years (2003-2007) and the later years (2008-2010). This breakdown into 3 groups reflects CDER McNeil interactions shown in Table 2. There was much CDER activity in the beginning period based on QA problems serious enough to warrant field alerts and recalls. Similarly during the end period of the study (2008-2010) there were also serious systemic problems that culminated in a FDA initiated court injunction to close the plant. In the middle years, there were significantly less problems noted, with no field alerts or recalls. It is the 5 year middle period that is of particular concern.

It raises these question:

- If QA and CAPA were adequately addressed in the initial years, why did they return later?
- Was there weakness in the FDA oversight mechanism?
- Did the manufacturer's solutions actually meet the FDA cGMP standard?

In sum, the researchers wanted to know in greater detail if the FDA oversight was proportional to McNeil's QA and CAPA failures.

The study period begins in 2000 with an EIR inspection, leading to a 483 report, and 2 field alerts. Then in 2001, the field alert expands into a recall. Yet there are no inspections in 2001 to investigate this situation. Actually for most of the study period (2000-2007), when CDER carried out inspections and found objectionable conditions, it gave the site 2 years to remedy the problem before it recommenced inspections. Furthermore, CDER often issued 483s in an 'on

again off again' fashion. There were 5 years where there were no 483s interspersed with 6 years when inspections yielded 483s. The underlined years show the absence of 483s (2000, 2001, 2002, 2003, 2004, 2005, 2006, 2007, 2008, 2009, 2010).

This runs counter to CDER best practices and cGMP methodology which specifically calls for increased focused activity based on the risk detailed in EIRs and 483s.

Then even more strikingly, at no time during this 11 year period that culminated in an injunction order to cease manufacturing and a plant closing, did CDER issue a warning letter. As discussed earlier, a WL is one of the FDA's principal enforcement tools used to establish prior notice before stringent enforcement or penalties are invoked. Without due diligence on the part of the FDA and McNeil, the manufacturing problems would tend to persist, and therefore the risks to the public would remain. By contrast, CDER in the last 3 years of this period (2008-2011) was proactive, following their own methodology, and did in fact exercise due diligence. Yet CDER still did not issue any warning letters.

Without WLs to review, the research then turned to 483 reports of objectionable QA conditions, particularly those between 2004-2011. As was mentioned earlier, in 2004 the FDA established the new cGMP standards emphasizing quality and CAPA activities. Therefore from 2004, the 483s would uniformly reference the same cGMP standards, and this would clarify the degree to which CDER exercised the necessary oversight. Table 3 addresses this by showing the persistent QA problems between 2004 and 2011.

Table 3 presents the contents from three reports: 483s for June 2004 and April 2010, and the Consent Decree of 2011. The contents of these documents have been summarized and the language modified for the sake of clarity. The table uses standard CDER categories: quality systems, packaging, laboratory, and facility and equipment systems. The recurrent theme in all three documents is that McNeil had substandard QA throughout its operations.

CDER determined that one of the main reasons for this inadequacy was that the quality control unit was not integrated with plant operations, and consequently failed to supervise, audit, and provide the necessary support. For instance, in the Quality Systems category there was failure to thoroughly review any unexplained discrepancy. Specifically, investigations did not always include appropriate QA documentation, nor were they timely or complete. That general lack of QA integration was repeated throughout the report, regardless of category.

Does this mean that after the detailed 2004 findings there was a dramatic improvement at Ft. Washington, then in the later period, an equally dramatic reversion to previous inferior standards? Or were CDER efforts at coaxing and providing 'soft' guidance, in fact unsuccessful? Or in fact, did certain interim inspections tend to be pro forma and lackadaisical as indicated by the brief 483 report of 2006 with only three observations?

Major Quality Assurance Functional Areas	483 June 2004	483 April 2010	Decree March 2011
Quality Systems			
a. Failure to thoroughly review any unexplained discrepancy. Specifically, investigations did not always include appropriate QA documentation, nor were they always timely or complete.	✓	✓	✓
b. Unexplained discrepancy did not extend to other drug products that may have been associated with the specific failure or discrepancy.	✓	✓	✓
c. Responsibilities and procedures applicable to the quality control unit are not in writing and fully followed.	✓	✓	✓
d. No written procedures for review of complaints, returned drug products, and conducting investigations.	✓	✓	✓
Packaging System			
e. Strict control is not exercised over labeling drugs products.	✓	✓	✓
f. Labeling and packaging materials are not representatively sampled and examined	✓	✓	✓
g. Quality Control unit did not review and approve procedures for packaging and reprocessing.	✓	✓	✓
Laboratory			
h. Batch production and control records do not include all necessary information.	✓	✓	✓
i. Laboratory records do not include necessary information: description of the sample received for testing, its source or location, the quantity and date of the sample.	✓	✓	✓
j. Quality control unit does not review or approve changes to equipment specifications or procedure.	✓	✓	✓
Facilities and Equipment System			
k. Written procedures are not established and followed for the cleaning and maintenance of equipment used in the manufacture, processing, packing or holding of drugs.	✓	✓	✓
l. Representative samples are not taken of each lot shipment for testing or examination.	✓	✓	✓

Table 3: QA Problems Between 2004 and 2011.

These somewhat rhetorical questions cannot be answered through one case study, particularly since the EIRs and the 483s were filled with much redacted material. Yet the idea that the site performed poorly at the beginning of the period, followed by dramatic improvements and then reversals, does not concur with known data on building sustainable QA (de Neufville, 2004). More information and insight are needed, and the 2011 Consent Decree to cease manufacturing provides some of that.

The Consent Decree addresses the same issues as in the 483s. In addition, it mandates that McNeil has the legal obligation to

- Hire a cGMP expert to ensure that the Ft. Washington manufacturing facility corrects deficiencies in methods, facilities, processes, and controls used to manufacture, process, pack, hold, and distribute drugs
- Develop a comprehensive, written quality assurance and quality control program that is adequate to ensure continuous compliance. This entails coordination with and appropriate oversight by the parent company, Johnson & Johnson
- Ensure the continuous compliance with the cGMP federal regulations relating to the safety, identity, strength, quality, and purity of drugs
- Have a Quality Control Unit, that is adequately qualified, trained and staffed to evaluate cGMP compliance on an ongoing basis to prevent and promptly correct future deviations

Faced with a recalcitrant McNeil, who were unable or unwilling to make the effort to achieve continuous compliance, CDER was fully challenged over the 12 year period. Like McNeil, CDER gives the impression that it was unable or unwilling to increase its oversight in terms of inspections, 483s, or WLs. Since CDER did not issue one WL to Ft. Washington over that time period, it would be hard to conclude that CDERs level of oversight was appropriate to the QA failures and dangers posed by Ft. Washington. Only in the last few years did CDER enforcement match the obdurance of McNeil.

Even the introduction of the new risk based cGMP in 2004 did not improve the overall safety of the plant, or strengthen the QA functions.

DISCUSSION

This research case study focused on one manufacturing facility within the BP sector. This targeted analysis spotlighted CDER activity over a 12 year period. Yet there are thousands of plants that produce finished pharmaceuticals. Therefore the findings by their very nature are limited, though arguably important for the following reasons:

- This is one of the few times the FDA has published EIRs and 483s showing their activity
- The McNeil facility produces popular non-prescription drugs: Motrin and Tylenol
- The plant has had recalls of millions of units over a 12 year period
- Johnson and Johnson, the parent company, has a well-established reputation for quality

While it is impossible to extrapolate from one case study, it is fair to ponder how CDER could fail to follow its own cGMP guidelines in facing this persistent series of QA failures. The same type of question may be asked about McNeil, one of the leading pharmaceutical manufacturers. There is no clearer indication of CDER procedural shortcomings than its failure to issue any WLs, the preliminary step for future enforcement activities (Goldstein, 2008). The researchers wanted to determine whether this lack of WLs was unique to the CDER-Ft. Washington interaction or was part of a larger trend in the BP sector for finished pharmaceuticals. To do this, the researchers reviewed WLs that meet the QA criterion of cGMP Part 211 based site inspections during the period 2003-2011.

This data was derived from the FDA document 2010 FDA's Field Activities—Office of Regulatory Affairs (United States Food and Drug Administration, Center for Drug Evaluation and Research, 2011) and other congressional reports (Crosse, 2008). These reports to Congress contain very useful data including budgetary and staffing information and field activities. Using these resources, it was straightforward to determine the total number of field inspections per year, as well as those that triggered WLs.

Table 4 shows CDER activity at facilities that manufacture finished pharmaceuticals. It displays the total number of inspections per year and WLs that were issued based on violations at those sites. During the time period 2003 to 2011, the number of inspections ranged from 983 and 1365, while the WLs from 13 to 48. Neither the number of WLs nor their percentages (Column C) seem particularly significant, given the large number of inspections. There does not seem to be any particular impact from the introduction of cGMP risk methodology in 2004. The WLs vary between 1% and 4% of the yearly inspections regardless of methodology. This modest number is in keeping with what we know regarding the FDA's problems of limited staff, budget, and resources that prevent the agency from expanding the number of inspection of manufacturing sites, regardless of methodology.

Year	(A)Total Inspections	(B)Part 211WLs	(C)Percent(B /A)
2003	1,149	35	3.0%
2004	1,232	26	2.1%
2005	1,365	14	1.0%
2006	1,222	20	1.6%
2007	1,073	13	1.2%
2008	972	29	3.0%
2009	983	26	2.6%
2010	1,174	48	4.0%
2011	983 *	38	4.2%*

* FDA estimate

Table 4: FDA Inspections (Part 211) and Corresponding WLs for the Finished Pharmaceutical Sector.

Facing the paucity of WLs throughout the sector, it is hard to argue that CDER is concentrating on the most risk prone manufacturers. Ft. Washington certainly is a good example of the latter. If CDER's objective is to use cGMP methodology to focus its limited resources on risk prone manufacturers, then there is seemingly a significant gap between the theory and practice. McNeil is a real world example of missing inspections, 483s, and WLs in spite of the objectionable conditions, field alerts and recalls.

Perhaps the focus should be moved from the cGMP risk methodology, to its implementation by CDER. One may plausibly argue that Ft Washington is in miniature a representation of CDER overall performance, with few inspections, and even fewer sites with WLs. In fact CDER may be so constrained that cGMP cannot be fully implemented.

Before more definitive statements can be made, supplemental topics need exploration. A broader research agenda may point to a different understanding of the FDA inspection process. For instance, additional information would include aggregation of the following BP sector information:

- CDERs actual enforcement policy
- The amount of experience and training inspectors have with CAPA and risk methodologies
- Specific data about product recalls, fines and penalties imposed by CDER
- Manufacturers' litigation history against the FDA

The researchers intend also to continue building other case studies to see if they in fact replicate the patterns shown in the Ft. Washington. With this type of research using case studies and broad sector analysis, the researchers are continuing to probe how CDER is meeting its workload, in spite of limited staff and resources, and its mandatory oversight within a technically and politically complex environment.

CONCLUSION

The current history of CDER-McNeil Ft. Washington in one sense confirms the budgetary and resource problems faced by the FDA. The McNeil case study puts a face on the decreasing CDER momentum, in terms of cGMP inspections and WLs. It also puts a face on the consequences to the public. Yet when the FDA does focus on a problem facility, as occurred in the last few years at Ft. Washington, its enforcement actions were clear and strong, forcing the plant to cease manufacturing. So we have a dual picture, one of CDER weighed by its constraints, the other sharply in focus when events get out of hand.

In summary, the inconclusive CDER activities at Ft. Washington (2000-2007):

- Inconsistent EIR inspections, in spite of field alerts and recalls
- Correspondingly, few 483 reports in spite of failure to remedy conditions
- Failure to issue cGMP WLs when facing persistent and significant QA problems

The more focused CDER enforcement (2008-2011):

- Frequent and rigorous inspections
- Detailed 483s documenting objectionable conditions
- Recalls on products
- Judicial Action through Consent Decree
- Forced plant closure

If the FDA is using the inspection process as a policy tool for guiding ‘willing’ manufacturers to more sustained compliance, then in this instance it has failed. Likewise, it should be noted in this case study that the more serious step of issuing 483s of objectionable conditions did not by itself trigger McNeil to remediate the CAPA problems.

This case study points to the fact that inspections and 483s are a ‘necessary but not sufficient’ activity by CDER. When faced with manufacturer’s recalcitrant behavior, WLs become an essential enforcement step. As a public document, the WL alerts the manufacturer and the consumer to flagrant quality control failures, and the possibility of legal action. With certain uncooperative manufacturers, this step has to become mandatory. When CDER fails to issue WLs necessary to protect the public safety, this conduct borders somewhere in the territory between negligence and incompetence.

The escalation of enforcement is clearly part of CGMP and CAPA methodologies, and therefore the issue in this case study is failure to implement procedures. The researchers in future studies would be interested in exploring the source of the failures. In addition to the budgetary and resource constraints mentioned earlier, other issues could be:

- Was CDER reluctant to go up against a Johnson and Johnson subsidiary, with its sophisticated legal staff?
- How many of McNeil current staff are former CDER employees? If the BP sector is a likely future employer for CDER staff, are there steps to safeguard the inspection process from favoritism?

Through additional case studies, the researchers plan to look deeper into those quality issues that have dogged McNeil, and should have been addressed more seriously by CDER.

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